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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/816,465	04/01/2004	Sonia Moreno-Lopez	MORENO-LOPEZ	8524

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ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/816,465	MORENO-LOPEZ ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment in response to the notice of non-compliant amendment received on 4/22/08 has been entered. Claims 1-41 are canceled and new claims 42-43 have been added. Claims 42-43 are currently pending in the instant application. An action on the merits follows.

Interview

The applicant provides their account of a telephonic interview that took place between this examiner and applicant's representative Dr. Zaghmout on 11/20/07. Applicant's account of the interview seems to indicate that the examiner agreed that the current amendments to the claims would place the claims in condition for allowance. This is inaccurate. During the interview, various potential claim amendments were discussed to try and differentiate the instant invention from the cited art of record. Limitations similar to the currently submitted added limitations were discussed, however, no agreement with regards to allowability of these claims was reached during this interview. The examiner repeatedly indicated that while these amendments might overcome the 102 rejection of record based on Schirmbeck, the examiner would need to conduct a new search and further indicated that the examiner was already aware of prior art that would most likely be applicable in a new 103 rejection of the claims. Therefore, it is reiterated that no agreement was reached during the interview of 11/20/07.

Priority

The previous office actions have acknowledged applicant's claim for foreign priority based on applications filed in Germany on October 2, 2001 or November 12, 2001, but noted that while the applicant has provided a certified copy of DE 101 56 678.6 in German, the office has only received a single cover page for DE 101 48 697.9, which does not constitute a certified copy. As indicated in the previous office action, a complete certified copy of DE 101 48 697.9 is required to fully comply with 35 U.S.C. 119(b).

The applicant has indicated that they are still trying to obtain the entire document, DE 101 48 697.9. However, as the entire document has not yet been received, the requirements for priority to DE 101 48 697.9 have not been met.

Claim Rejections - 35 USC § 102

The rejection of claim 41 under 35 U.S.C. 102(a) as being anticipated by Schirmbeck et al. (June 2001) J. Mol. Med., Vol. 79, 343-350, is withdrawn over canceled claim 41 and is newly applied to new claim 43. Applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

Please note that as discussed in the new rejection of claims 42-43 below under 35 U.S.C. 112, second paragraph, claim 43 as written is confusing and indefinite in that it appears to comprise one defined method step and one undefined method step. The method as claimed recites a first method step (a) in which the MIDGE-NLS encoding HBsAG is "administered" to the subject. The method then recites a step (b) "injecting intradermally into a living being to

protect against infectious diseases caused by intracellular infection germs". The second method step does not identify what is to be injected intradermally into the living being. In the interests of compact prosecution, the claim has been interpreted to read on administering the MIDGE-NLS encoding HBsAG by any route of administration, including but not limited to intradermal injection.

The rejection of record as it applies to new claim 43 is set forth as follows. Schirmbeck et al. teaches a minimal expression construct (MIDGE) comprising covalently closed linear DNA that contains only a hepatitis B surface antigen (HBsAG) coding sequence operably linked to CMV promoter and polyA termination sequence where the linear ends are linked by short single stranded loops of DNA, and wherein the construct is further covalently linked to the nuclear localization sequence (NLS) oligopeptide PKKKRKVEDPYC (Schirmbeck et al., page 345, Figure 1 B.3). Schirmbeck et al. also teaches a vaccine comprising this construct, and methods of inducing hepatitis antigen specific immune response in vivo by intradermal or intramuscular injection of the MIDGE-peptide vaccine (Schirmbeck et al., page 346 and 348). Note as well that Schirmbeck et al. demonstrates that the MIDGE-NLS construct can induce "type 1-cellular mediated immune responses" depending on the route of administration such that the MIDGE-NLS construct encoding HBsAG meets the claim limitation that of a "type 1-cellular mediated immune-response eliciting vaccine". Thus, by teaching all the limitations of the claims as written, Schirmbeck et al. anticipates the instant invention as claimed.

The applicant argues that the claim has been amended to recite the limitations of previously pending claims 41 and 38 and that the examiner "agreed to the proposed claims" of this scope with the proviso that the term "comprising" would require additional consideration.

The details of the interview were discussed above. It is reiterated that no agreement was reached regarding any proposed claim amendments. The applicant further argues that Schirmbeck et al. does not teach intradermal administration. However, as can be seen from the previous paragraph which sets forth the teachings of Schirmbeck et al., Schirmbeck et al. clearly teaches an NLS oligopeptide comprising PKKKRKV (SEQ ID NO:3), see especially the underlined amino acids in the NLS used by Schirmbeck et al.. Further, Schirmbeck et al. clearly teaches intradermal administration as a route of administration (Schirmbeck et al. pages 346, 348). Further, as noted above, the claim as written simply specifies that the MIDGE-NLS construct encoding HBsAG to be administered is a "type 1-cellular mediated immune-response eliciting vaccine". The results of Schirmbeck et al. show that the MIDGE-NLS construct encoding HBsAG disclosed by Schirmbeck et al. can in fact induce CTL responses. Therefore, the rejection of record stands over new claim 43.

Applicant's addition of new claim 42 has necessitated the following new grounds of rejection under 35 U.S.C. 103(a).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 42 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over Schirmbeck et al. (June 2001) J. Mol. Med., Vol. 79, 343-350, in view of Makkerh et al. (1996) Current Biology, Vol. 6(8), 1025-1027.

Please note that as discussed in the new rejection of claims 42-43 below under 35 U.S.C. 112, second paragraph, claim 42 as written is confusing and indefinite in that it appears to comprise one defined method step and one undefined method step. The method as claimed recites a first method step (a) in which the MIDGE-NLS encoding HBsAG is "administered" to the subject. The method then recites a step (b) "injecting intradermally into a living being to protect against infectious diseases caused by intracellular infection germs". The second method step does not identify what is to be injected intradermally into the living being. In the interests of compact prosecution, the claim has been interpreted to read on administering the MIDGE-NLS encoding HBsAG by any route of administration, including but not limited to intradermal injection.

Schirmbeck et al. teaches a minimal expression construct (MIDGE) comprising covalently closed linear DNA that contains only a hepatitis B surface antigen (HBsAG) coding sequence operably linked to CMV promoter and polyA termination sequence where the linear

ends are linked by short single stranded loops of DNA, and wherein the construct is further covalently linked to the nuclear localization sequence (NLS) oligopeptide PKKKRKVEDPYC (Schirmbeck et al., page 345, Figure 1 B.3). Schirmbeck et al. also teaches a vaccine comprising this construct, and methods of inducing hepatitis antigen specific immune response in vivo by intradermal or intramuscular injection of the MIDGE-peptide vaccine (Schirmbeck et al., page 346 and 348). Note as well that Schirmbeck et al. demonstrates that the MIDGE-NLS construct can induce "type 1-cellular mediated immune responses" such as a CTL response depending on the route of administration such that the MIDGE-NLS construct encoding HBsAG meets the claim limitation that of a "type 1-cellular mediated immune-response eliciting vaccine".

Schirmbeck et al., while teaching an SV40 derived NLS comprising PKKKRKV does not teach a specific NLS of 5-25 amino acids where at least half of the amino acids are K or R. However, at the time of filing, the exact nuclear localization sequence (NLS) of SV40 was known. Makkerh et al. teaches that the sequence consisting of PKKKRKV is the defined nuclear localization sequence of SV40, which can be used to target heterologous molecules to the nucleus (Makkerh et al., page 1025, and Table I, page 1027). PKKKRKV is an oligopeptide between 5 and 25 amino acids which contains more than 50% K and R residues.

Therefore, based on the teachings of Schirmbeck et al. to covalently attach a peptide such as an NLS derived from SV40 comprising the sequence PKKKRKV, and the teachings of Makkerh et al. that the minimal sequence of the NLS peptide from SV40 useful for targeting molecules to the nucleus is PKKKRKV, it would have been *prima facie* obvious to the skilled artisan at the time of filing to use a MIDGE encoding HBsAG covalently linked to the defined NLS peptide PKKKRKV of Makkerh et al. in the methods of inducing immune responses to

HBsAg taught by Schirmbeck et al. Further, based on the teachings of both Schirmbeck et al. that the SV40 derived NLS functions successfully to target DNA to the nucleus, the skilled artisan would have had a reasonable expectation of success in utilizing a MIDGE encoding HBsAg covalently linked to PKKRKV to induce immune responses against HBV in a subject. Note as well that such as substitution of PKKKRKV for PKKKRKVEDPYC represents nothing more than choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success. See *KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (2007),* and *Alza Corp. v. Mylan Laboratories, Inc. 464 F. 3d 1286, 80 USPQ2d 1001 (Fed. Cir. 2006).*

Claim Rejections - 35 USC § 112

The rejection of previously pending claim 41 under 35 U.S.C. 112, second paragraph, for indefiniteness is withdrawn in view of the cancellation of this claim.

Applicant's addition of new claims 42-43 necessitated the following new grounds of rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 42-43 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 42-43 recite appear to recite two method steps, where the first method step (a) recites administering a therapeutic amount of a product where the product is a MIDGE-NLS encoding HBsAG, and the second step (b) recites "injecting intradermally into a living being to protect against infectious diseases caused by intracellular infection germs". The second method step does not identify what is to be injected intradermally into the living being. As such, the metes and bounds of the claim cannot be determined as it is completely unclear what exactly is to be injected intradermally into the living being. Further, it is unclear whether applicant intended to further limit the administration step of (a) to intradermal injection or whether applicant intended to claim a two part vaccination methodology where the MIDGE is administered by any route followed by administration of the same MIDGE or some other product intradermally. In the interests of compact prosecution, the claims have been interpreted to read on administering the MIDGE-NLS encoding HBsAG by any route of administration, including but not limited to intradermal injection.

Claims 42-43 are not allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633